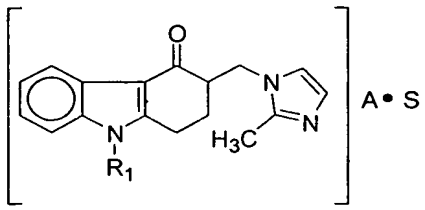
REMARKS

Claims 1-4 and 9 have been cancelled, without prejudice. Claims 22 and 72 have been amended to correct typographical errors. Applicants thank the Examiner for pointing out the misspelling in claim 72. Although claim 18 also was objected to on the grounds that it contains a misspelling, Applicants do not believe claim 18 contains a spelling error. There appears to be an alternative spelling "sonocation" for the word "sonication" which appears in claim 18. However, the alternative spelling does not appear to have a wider acceptance than Applicants' spelling and accordingly claim 18 has not been amended. If the Office sustains the objection, Applicants will comply and amend claim 18 to conform to the Examiner's preferred spelling. Multiply dependent claim 23 has been amended to correct an error in the dependency. As amended, claim 23 depends from claims 19-22. Claims 5-8 and 10-93 are pending.

1. The Cited Art

The Examiner relies on Wu Gousheng et al. (CN1113234A) as the sole reference for rejecting Applicant's claims under 35 U.S.C. §§ 102(b) and 103. In applying the reference under § 102, the Examiner points to the alleged disclosure by Wu Gousheng of ondansetron hydrochloride monohydrate obtained by recrystallization from water in Embodiment A_1 (p. 8, lines 22-24 of the translation). The Examiner also relies upon the abstract on page one of the translation for its teaching that "an organic base and standard physiological salt and solvate can be incorporated in the compound in order to be used as a medication for treating nausea and vomiting." (Action mailed 1/6/03, p. 2). The abstract of Wu Gousheng is not self-contained. It refers to "a chemical compound with chemical structural formula (I)" which is

found on page 1 of the description and in claim 1. Structural formula (I) is reproduced below.



In formula (I), variable "A" is defined as "hydrochloric acid, sulfuric acid, hydrobromic acid, oxalic acid, maleic acid, inorganic acids(s), or organic acid(s)." Accordingly, variable "A" could be any of these acids. Variable "S" represents water. Neither formula (I) nor the definitions indicate a particular quantity of water that is present in compounds of formula (I). In addition, Wu Gousheng discloses in Formula X the known ondansetron hydrochloride dihydrate.

The Examiner's comment that Applicants' solvent systems are similar in functionality to the Wu Gousheng's benzene/n-propanol system (Action 1/6/03, p. 5) is misplaced. Wu Gousheng employs those solvents as part of the synthesis; while, Applicants utilize them for crystallization.

Turning to the specific "Embodiments," a.k.a. examples, of Wu Gousheng, Embodiment A_2 (translation p. 10) purportedly yields a monohydrate of ondansetron hydrochloride by placing ondansetron hydrochloride dihydrate in a dryer containing P_2O_5 under vacuum. Embodiment B produces ondansetron hydrochloride dihydrate. Embodiments C, D, E and F produce ondansetron free base and the last embodiment, G, produces a compound with a different covalent structure from ondansetron. The Wu Gousheng reference also discusses preparative methods for making ondansetron free base and related compounds which are not believed to have been relied upon in this Action.

2. **Rejection under 35 U.S.C. § 102**

Claims 1-4, 9, 19-23, 39-45, 49-50, 52, 57, 58, 62-67, 71 and 87-91 have been rejected as being allegedly anticipated by Wu Gousheng.

Claims 1, 2 and 9 of this application directed to ondansetron hydrochloride monohydrate and same containing about 5% or 5-10% water have been cancelled without prejudice.

In support of the rejection of claims 3 and 4, the Examiner further asserts that the X-ray diffraction properties recited in those claims are inherently present in the ondansetron hydrochloride monohydrate obtained by following the teachings of Wu Gousheng. (Action mailed 1/6/03, p. 2). Applicants have performed the procedures for making ondansetron hydrochloride monohydrate in Wu Gousheng and determined its polymorphic identity in order to determine whether the Examiner had a reasonable basis in fact for the inherency rejection. The declarations of inventors Revital Lifshitz (Exh. 1) and Judith Aronhime (Exh. 2) submitted herewith attest to the correctness of the Examiners position. Accordingly, claims 3 and 4 have also been cancelled.

Claims 19-23, 39-45, 49-50, 52, 57, 58, 62-67, 71 and 87-91 are pending and also have been rejected for anticipation over Wu Gousheng. Applicants traverse rejection of those claims.

Claims 19 and 20 are directed to anhydrous ondansetron hydrochloride. "A claim is anticipated only if each and every element as set forth in the claim is found either expressly or inherently described, in a single prior art reference." MPEP § 2131 (Aug. 2001), *quoting*, *Verdegall Bros. v. Union Oil co. of California,* 814 F.2d 628 631 (Fed. Cir. 19887) Thus, to be proper, a rejection of claims 19 and 20 for anticipation requires that Wu Gousheng disclose ondansetron hydrochloride that is anhydrous, either expressly or inherently. Wu

Gousheng neither discloses nor enables anhydrous ondansetron hydrochloride. Not a one of the Embodiments of Wu Gousheng that yields ondansetron hydrochloride (Embodiments A_1, A_2 and B) yields it in an anhydrous state. In each such instance, it is obtained either in a monohydrate or dihydrate state. Wu Gousheng's disclosure relating to ondansetron hydrochloride monohydrate and dihydrate does not anticipate anhydrous ondansetron hydrochloride because they are not anhydrous. The abstract upon which the Examiner relies does not anticipate claims 19 and 20, *inter alia*, because it merely speaks of the utility of a general class of hydrated salts encompassed by formula (I), not anhydrous ondansetron hydrochloride. For the foregoing reasons, the rejection of claims 19 and 20 under 35 U.S.C. § 102(b) is improper and should be withdrawn.

In addition, drying of dihydrate crystals over P_2O_5 while under vacuum (extremely desicating conditions), failed to completely dehydrate the dihydrate crystals, producing instead the monohydrate. Assuming, *arguendo,* that Wu Gousheng did disclose anhydrous ondansetron hydrochloride, it clearly does not enable one of ordinary skill in the art to make it. For this reason also, the rejection of claims 19 and 20 under 35 U.S.C. § 102(b) is improper and should be withdrawn.

The rejection of claims 21 and 22 directed to ondansetron hydrochloride Form B characterized by certain enumerated PXRD characteristics under 35 U.S.C. § 102(b) also is improper and should be withdrawn. Wu Gousheng does not disclose ondansetron hydrochloride Form B as defined in claims 21 and 22. Wu Gousheng does not expressly anticipate these claims because Wu Gousheng does not contain any powder X-ray diffraction analysis of ondansetron hydrochloride. Moreover, Wu Gousheng also does not anticipate these claims inherently. Wu Gousheng teaches the preparation of ondansetron hydrochloride in only two hydrated solid states: a monohydrate and a dihydrate. X-ray diffraction patterns

are inherently present in a compound, as the Examiner has noted. As the Examiner contends and Applicants have confirmed, the ondansetron hydrochloride monohydrate obtained by following the teachings of Wu Gousheng possesses the X-ray diffraction properties shown in Appendix A of the Declaration of Judith Aronhime and Figure 1 of Applicants' application and produces a PXRD pattern with peaks at 6.1, 12.4, 17.0, 18.3, 19.2, 20.3, 20.9, 24.1, 23.3 24.8, 28.1 and 30.3±0.2 °2θ. (Application, p. 6, lines 5-8)

"The existence of polymorphs is best established by x-ray crystallographic examination." Byrn, S.R. *Solid-State Chemistry of Drugs* p. 79 (Academic Press 1982).

> X-ray powder diffraction is perhaps the "gold standard" for the qualitative determination of crystallinity. Not only can the presence of a crystalline phase be confirmed, but since each polymorph produces a unique diffraction pattern, the question of which polymorph crystallized can be addressed.

Brittain, H.G., *Polymorphism in Pharmaceutical Solids* p. 398-99 (Marcel Dekker 1999) (Excerpts attached as Exh. 3).

Comparison of the peak listing or X-ray pattern of ondansetron hydrochloride monohydrate with claims 21 and 22 clearly shows that Form B is a distinctly different solid state of ondansetron hydrochloride from the ondansetron hydrochloride monohydrate product of Wu Gousheng. To mention but a few differences, the monohydrate prepared by following the teachings of Wu Gousheng does not produce powder X-ray diffraction peaks at 10.5, 13.0, 13.5 and 15.1±0.2 °2θ.

"The most useful method to compare X-ray powder diffraction data obtained from different samples and on the same instrumentation is to overlay and align the respective films or plots." Byrn, S.R. et al. *Solid-State Chemistry of Drugs* 2nd ed. 63 (SSCI: West Lafayette, Indiana 1999) (Excerpts provided as Exh. 4).

> [C]omparisons of peak positions and intensities may fall anywhere between complete agreement to complete disagreement of the patterns. In either of these extreme cases, the respective conclusions are, of course, unequivocal: the structures are the same or they are different.

Id.

Applicants' Fig. 1 and Fig. 2 are reproduced below.

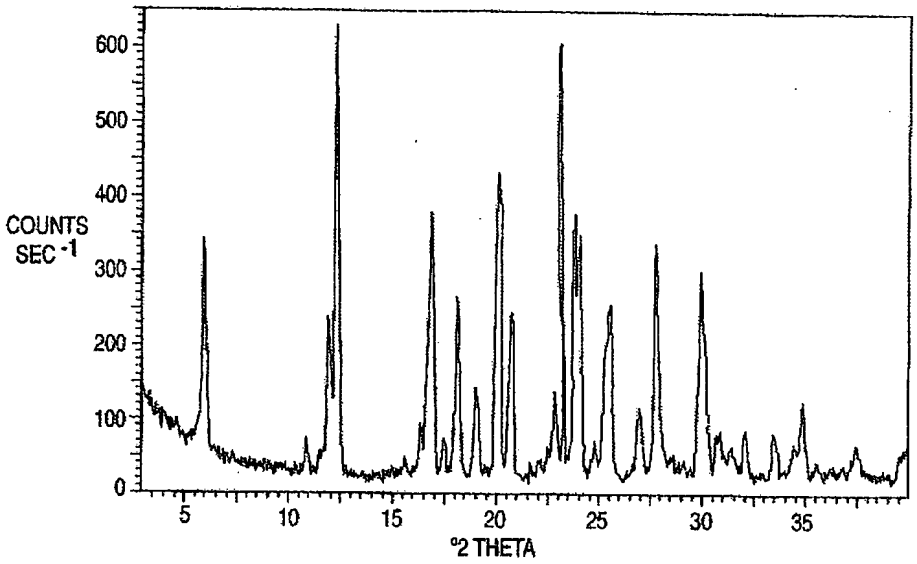


FIG. 1

Applicants' Fig. 1: PXRD pattern of ondansetron hydrochloride monohydrate.

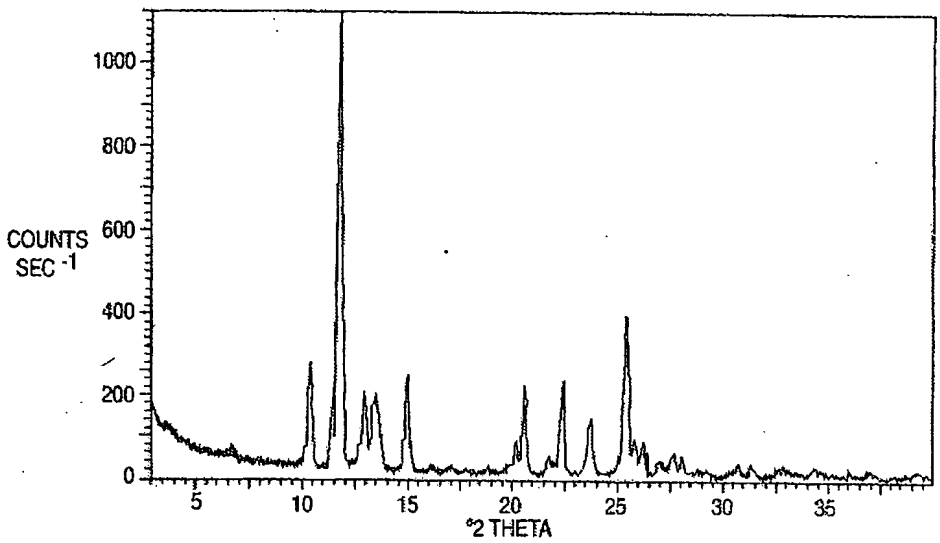


FIG. 2

Applicants' Fig. 2: PXRD pattern of ondansetron hydrochloride Form B

As shown in Fig. 1 and stated in the application, ondansetron hydrochloride monohydrate produces a strong X-ray peak at 23.3±0.2 °2θ. (p. 6, lines 5-8) Turning to Figure 2 of the application it can be clearly seen that Form B does not produce a strong peak at that position. Further, side-by-side comparison of Figure 2 with the powder X-ray diffraction pattern of ondansetron hydrochloride monohydrate clearly shows that the monohydrate and Applicants' Form B are different solid states of ondansetron hydrochloride. Ondansetron hydrochloride monohydrate and Form B present an extreme case where the conclusion is unequivocal. The crystal structures are different.

As stated in Applicants' specification, ondansetron hydrochloride dihydrate produces a powder X-ray diffraction pattern essentially the same as the pattern shown in Figure 1 (p. 3, lines 19, 20). Accordingly, Form B and ondansetron hydrochloride dihydrate also are unequivocally different.

Multiply dependent claim 23 directed to a pharmaceutical composition comprising ondansetron hydrochloride has been amended to reduce the number of claims from which it

depends to claims 19-22. As amended, the rejection of claim 23 cannot be sustained, *inter alia*, for the same reasons that rejection of claims 19-22 cannot be sustained. The active ingredient is novel.

Claims 39-44 directed to ondansetron hydrochloride Form B of a particular particle size, and pharmaceutical compositions thereof also are not anticipated, *inter alia*, for the same reasons that claim 21 is not anticipated. Ondansetron hydrochloride Form B is novel.

Claim 45 is directed to anhydrous ondansetron hydrochloride Form B with a water content up to about 2%. Claim 45 expresses the fact that particles of an anhydrous crystalline material having adventitious water adsorbed onto their surfaces can hold up to 2% of their weight of water. Claim 45 is not anticipated for the same reason that claim 19 directed to anhydrous ondansetron hydrochloride is not anticipated (supra pp. 5 and 6).

Claims 49 and 50, directed to ondansetron hydrochloride Form C, were rejected under 35 U.S.C. § 102(b) over Wu Gousheng. The deficiencies of Wu Gousheng as an anticipatory reference have been previously discussed in relation to claims 21 and 22 (supra p. 6 et seq.). The ondansetron hydrochloride obtained by following the teachings of Wu Gousheng also does not meet all the limitations of claims 49 and 50. Comparison of the powder X-ray diffraction pattern of ondansetron hydrochloride monohydrate (p. 6, lines 5-8) with claims 49 and 50 shows that Form C is distinctly different from the known ondansetron hydrochloride monohydrate and dihydrate.

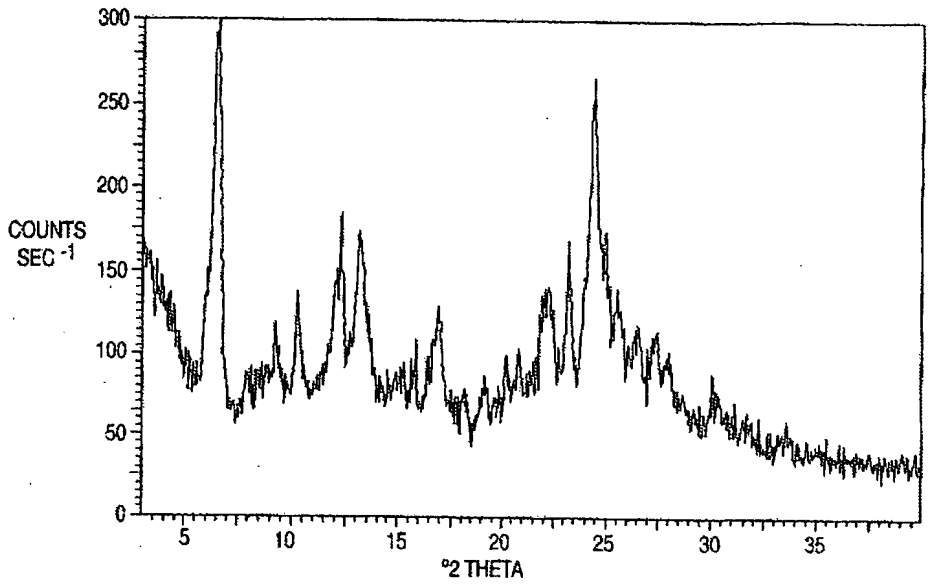


FIG. 3

Applicants' Fig. 3: PXRD pattern of ondansetron hydrochloride Form C

For instance, the hydrates known to the art do not produce powder X-ray diffraction peaks at 9.2, 10.2, 13.1 and 24.4±0.2 °2θ. Further, side-by-side comparison of Figure 3 with Figure 1 confirms that Form C is unequivocally a different solid state of ondansetron hydrochloride from these known hydrates. Therefore, Applicants respectfully request that the rejections of claims 49 and 50 for anticipation over Wu Gousheng be reconsidered and withdrawn.

Claim 52 is directed to ondansetron hydrochloride Form D. Wu Gousheng likewise does not expressly disclose Form D or teach a process that would inherently produce ondansetron hydrochloride meeting all of the limitations of claim 52. For instance, the monohydrate and dihydrate do not produce powder x-ray diffraction peaks at 8.3, 14.0 and 14.8±0.2 °2θ. Therefore, reconsideration and withdrawal of the rejection of claim 52 is respectfully requested.

Claims 57 and 58 are directed to ondansetron hydrochloride Form E. Wu Gousheng does not expressly disclose ondansetron hydrochloride meeting all of the limitations of these

claims, nor would one obtain such a material by following the teachings of Wu Gousheng. Comparison of Figure 1 with claims 57 and 58 or Fig. 4 unequivocally shows that Form E is a distinctly different solid state of matter from the known monohydrate and dihydrate

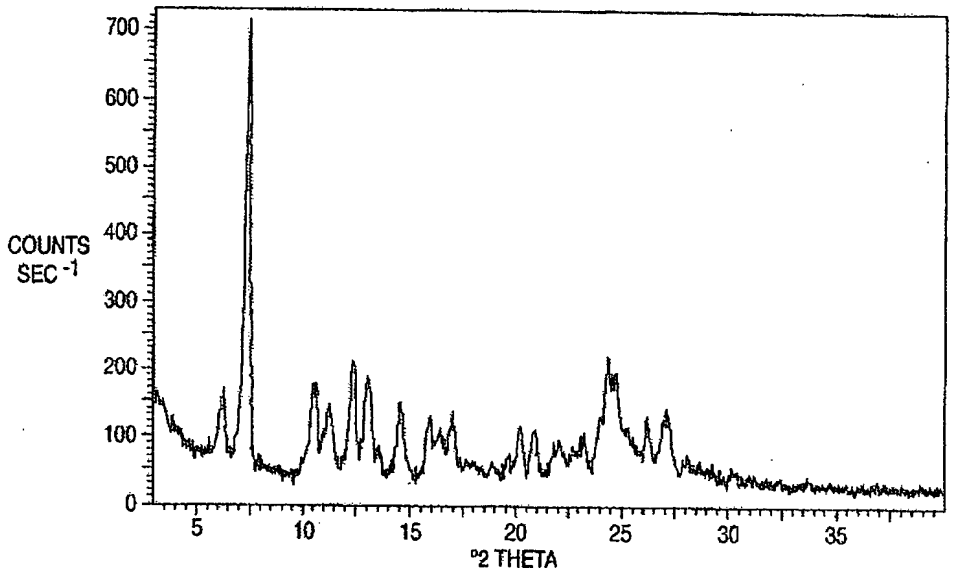


FIG. 4

Fig. 4: PXRD pattern of ondansetron hydrochloride Form E

For instance, the monohydrate and dihydrate do not produce powder X-ray diffraction peaks at 10.5, 14.5 and 15.9±0.2 °2θ to list just a few of the limitations of these claims that are not met by the reference.

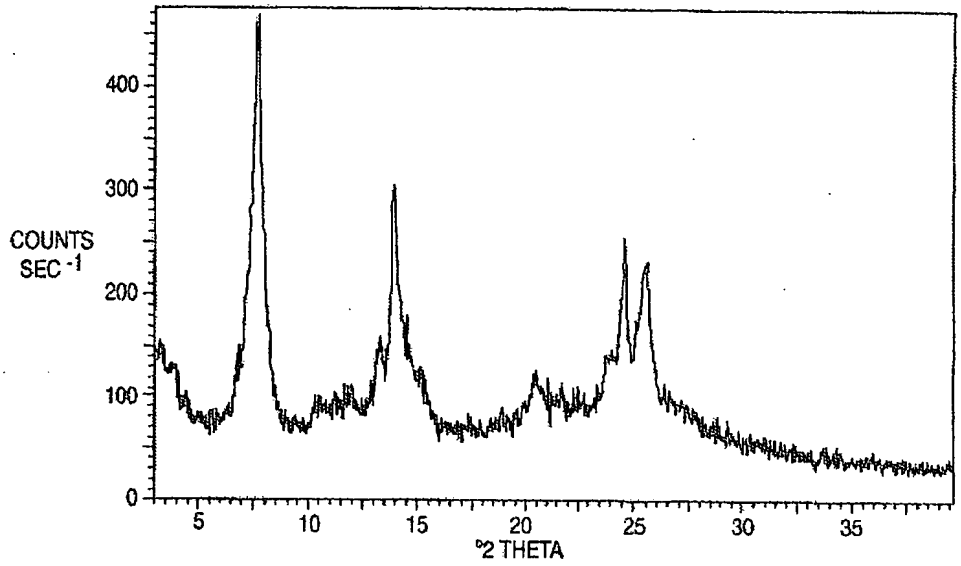


FIG. 6

Fig. 5: PXRD pattern of ondansetron hydrochloride Form H

Therefore, the rejection of claims 57 and 58 under 35 U.S.C. § 102(b) also is improper and should be withdrawn.

Claims 62-66 are directed to ondansetron hydrochloride isopropanolate, an isopropanol solvate of ondansetron hydrochloride. Wu Gousheng does not expressly disclose ondansetron hydrochloride isopropanolate. Moreover, Wu Gousheng does not teach the use isopropanol for any purpose. Thus, under no circumstance would one following the express teachings of Wu Gousheng produce ondansetron hydrochloride isopropanolate, let alone do so inherently. Accordingly, reconsideration and withdrawal of the rejection of claims 62-66 under 35 U.S.C. § 102(b) is respectfully requested.

Claim 67 is directed to ondansetron hydrochloride Form H. Wu Gousheng does not expressly disclose Form H or teach a process that would inherently produce ondansetron hydrochloride meeting all of the limitations of claim 67. For instance, the monohydrate and dihydrate one obtains by following the teachings of Wu Gousheng do not produce powder X-

ray diffraction peaks at 7.8, 14.0 and 14.8±0.2 °2θ. Therefore, reconsideration and withdrawal of the rejection of claim 67 under 35 U.S.C. § 102(b) is respectfully requested.

Claim 71 directed to pharmaceutical compositions comprising novel ondansetron hydrochloride polymorphs and solvates is novel for the same reasons that claims 49, 50, 52, 57, 58 and 62-67 directed to those solid state forms are novel. Therefore, the rejection of claim 71 for anticipation also is improper and should be withdrawn.

Claims 87-91 are directed to ondansetron hydrochloride of particular particle sizes and pharmaceutical compositions comprising ondansetron hydrochloride of particular particle sizes. Wu Gousheng is silent regarding the particle size of ondansetron hydrochloride obtained by following its teachings.

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such a gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference . . .

MPEP § 2131.01 (Aug. 2001), *quoting*, *Continental Can Co. USA v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991)

Since Wu Gousheng is silent regarding particle size it is not an anticipatory reference to claims 87-91 unless combined with extrinsic evidence that makes clear that ondansetron hydrochloride prepared following the teachings of Wu Gousheng would necessarily have a particle size below 200, 100 and 50 μm. The Examiner has not put forth such extrinsic evidence and for that reason alone the rejection of claims 87-91 under 35 U.S.C. § 102(b) is improper and should be withdrawn.

Claims 72-76 and 93, were not rejected in the Office Action. However, they were not indicated as allowed in the Office Action Summary either. Applicants offer the following

remarks in the event that the Examiner intended to reject these claims on grounds relied upon to rejected Applicants' other claims under § 102(b).

Claims 72 and 73 are directed to ondansetron hydrochloride methanolate, a methanol solvate of ondansetron hydrochloride. Wu Gousheng does not expressly disclose ondansetron hydrochloride methanolate nor does Wu Gousheng disclose or teach the use of methanol in any way that could lead to the production of solid ondansetron hydrochloride. The recrystallization of ondansetron free base from methanol in Embodiments B, C_1, C_2 and E, of Wu Gousheng, followed by drying would not produce ondansetron *hydrochloride* methanolate and it is unclear from the disclosure whether a methanol solvate of the free base was obtained. One following the teachings of Wu Gousheng would not produce a methanol solvate of ondansetron hydrochloride, even occasionally, let alone inherently. Therefore, the rejection of claims 72 and 73 under 35 U.S.C. § 102(b) is improper and should be withdrawn.

Claims 74-76 are directed to ondansetron hydrochloride Form I which is capable of existing as a methanol solvate. Wu Gousheng does not disclose ondansetron hydrochloride Form I as expressed in claims 74-76. The ondansetron hydrochloride monohydrate and dihydrate disclosed by Wu Gousheng do not meet all of the limitations of claims 74, 75 and 76, as can be appreciated by comparing those claims with Appendix A of the Declaration of Judith Aronhime submitted herewith, Figure 1 of Applicants' application, or the peak listing on p. 6, lines 5-8, of the application. For instance, the known hydrates of ondansetron hydrochloride do not produce X-ray peaks at 8.2, 9.3 and 9.9±0.2 °2θ. In addition, comparison of Figure 1 with the PXRD pattern of Form I in Fig. 7 also shows that they are distinctly different crystalline materials.

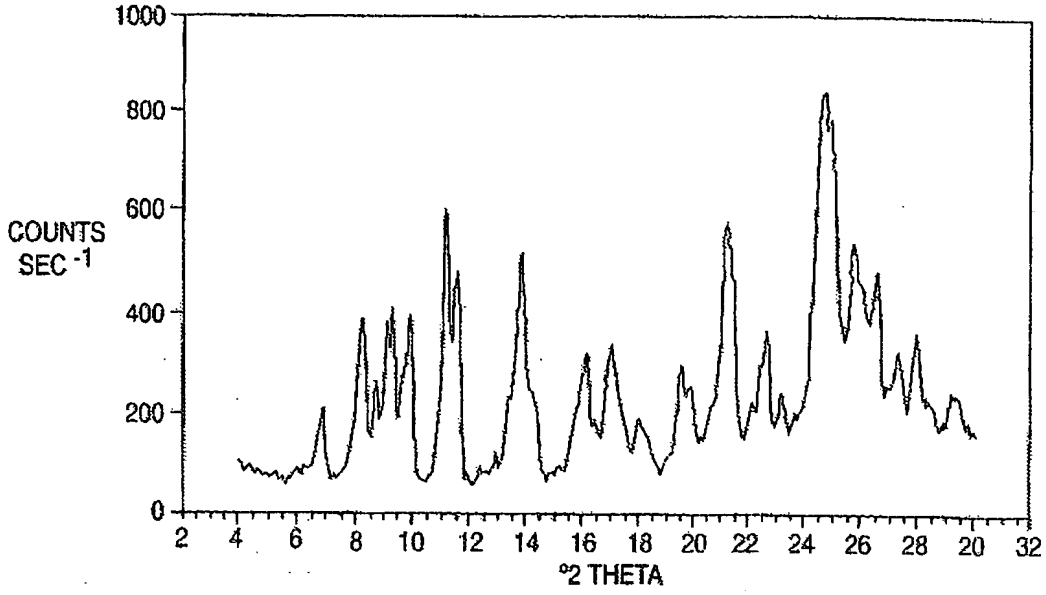


FIG. 7

Applicants' Fig. 7: PXRD pattern of ondansetron hydrochloride Form I

Claim 93, directed to a pharmaceutical composition containing ondansetron hydrochloride Form I also is allowable for the same reason claim 74, directed to the active ingredient is allowable.

For the foregoing reasons, Applicants respectfully submit that the anticipation rejection as applied to claims 19-23, 39-45, 49-50, 52, 57, 58, 62-67, 71 and 87-91 cannot be sustained under the proper legal standard of anticipation which requires consideration of all limitations of a claim.

3. Rejection under 35 U.S.C. § 103(a)

The Examiner has not asserted that Applicants' claims directed to ondansetron $HCl \cdot H_2O$, Form A, anhydrous ondansetron HCl, and Forms B, C, D, E, H and I are obvious over Wu Gousheng. Based upon the withholding of an obviousness rejection of claims 1-4, 9, 19-23, 39-45, 49-50, 52, 57, 58, 62-67, 71 and 87-91, Applicants understand the Examiner's

view to be that Wu Gousheng would not render obvious any of Applicants' composition of matter claims that is found to be novel over Wu Gousheng. Applicants agree with this view. It is well recognized that the solid state behavior of molecules is highly unpredictable. "No rules exist that allow prediction of whether a compound will exhibit polymorphism however, polymorphism is widespread in pharmaceuticals, particularly in steroids, sulfonamides, and barbiturates." Byrn, S.R. *Solid-State Chemistry of Drugs* p. 7 (Academic Press 1982) (Excerpts provided as Exh. 5). "Until that time [that computer programs are able to predict stable crystal forms] the development scientist is handicapped in attempting to predict how many solid forms of a drug are likely to be found." Brittain, p. 185 (Exh. 3). "With the advent of molecular modeling techniques for crystal growth prediction, interest has been generated in the computer prediction of polymorphism. [fn] The task is difficult because of the lacunae in our understanding of polymorph structure." Threlfall, T.L. *Analyst*, 1995, *120*, 2433, 2438 (Exh. 6).

Claims 5-8, 10-18, 24-38, 46-48, 51, 53-56, 59-61, 68-70, 77-86 and 92, have been rejected as being unpatentable for obviousness under 35 U.S.C. § 103(a) over Wu Gousheng. Collectively, these claims are to processes for making and methods of use of Applicants' claimed compositions of matter.

A *prima facie* case of obviousness has three criteria. "First, there must be some suggestion or motivation, either in the references themselves or in the knowledge available to one of ordinary skill in the art, to modify the reference or to combine reference teachings." Second, a reasonable expectation of success must exists. Third, the prior art must teach or suggest all claim limitations. MPEP § 2142. "The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." MPEP § 2143.

The Examiner notes that Applicants' process claims recite specific conditions whereby each of the claimed ondansetron HCl polymorphs can be prepared. (Action, p. 5) For instance, the Examiner notes that in some processes, particular solvents are used (Action p. 5 lines 1-4), that there are preferred operating temperatures for some of the processes and that sometimes mechanical agitation is preferred. Each of the broadest claims to processes for making each polymorph is distinct from the others as shown in the following Table.

Monohydrate	Form A	Form B	Form C	Form D	Form E	Form H	Form I
Claim 5 a) contacting crystals of ondansetron hydrochloride dihydrate with a mixture of from about 4% to about 50 % water in ethanol, b) separating the ethanol:water mixture, and c) recovering the crystals as ondansetron hydrochloride monohydrate.	Claim 8 a) providing crystals of the ondansetron hydrochloride monohydrate of claim 1, b) hydrating the crystals under an atmosphere of 50% relative humidity or greater, and c) collecting the hydrated crystals containing about 10% water of crystallization. Claim 10 a) suspending ondansetron free base in a liquid medium selected from the group consisting of absolute ethanol, a mixture of ethanol and isopropanol, and chloroform, b) dissolving the free base by adding anhydrous HCl to the suspension, c) crystallizing ondansetron hydrochloride from the liquid medium, and d) separating the crystals from the liquid medium. Claim 16 a) dehydrating crystals of ondansetron hydrochloride dihydrate by contacting with a liquid medium selected from the group consisting of ethanol, mixtures of ethanol and water, toluene and mixtures of ethanol and toluene, b) separating the liquid medium from the crystals, and c) collecting the crystals.	Claim 46 reacting HCl gas with a toluene solution of ondansetron base.	Claim 51 a) dissolving ondansetron base in ethanol, b) adding an ethanolic solution of hydrochloride, c) filtering, and d) evaporating the mother liquor.	Claim 53 a) melting ondansetron hydrochloride in the presence of xylene; and b) adding the melt to ethanol.	Claim 59 treating ondansetron hydrochloride in isopropanol.	Claim 68 a) suspension of ondansetron base in absolute ethanol; b) adding an ethanol solution of hydrochloric acid; c) precipitating with the addition of ether; and d) isolating the product.	Claim 77 exposing ondansetron hydrochloride to methanol vapor.

Each of the broadest process claims sets forth a procedure discovered by the Applicants that is adapted to produce a particular solid state of ondansetron hydrochloride with distinct physical properties. Evidently relying upon hindsight reconstruction, the Examiner has not considered each of Applicants process claims in their entirety wherein procedures are set forth to obtain different solid state forms of ondansetron hydrochloride.

The Examiner relies upon Wu Gousheng alone in rejecting Applicants' process claims under § 103(a). The Examiner finds in Wu Gousheng Embodiment B that ondansetron hydrochloride is made by bubbling HCl gas through a solution of ondansetron in ethanol. Afterwards, the mixture is cooled to maximize recovery of the ondansetron HCl.
The Examiner also asserts that benzene and n-propanol are used in Wu Gousheng . (Action, p. 5, lines 5-7). It is asserted that "benzene and n-propanol are similar to the functionality of the claimed solvents." Since different products are obtained, *ipso facto*, the solvents identified in the claims are not at all "similar to the functionality" of the solvents which Applicants have discovered yield novel solid state forms of ondansetron hydrochloride. If they were functionally equivalent as the Examiner contends, then new materials would not be obtained by using them. The following are examples taken from the literature which are not in accord with the Examiner's view that different solvents have similar functionality. As these Examples further show, the simple notion that one can control the hydration state of compound by routine adjustment of the amount of water in the solvent from which the compound is crystallized is at its core unreliable.

> An anhydrous form of cortisone acetate (Form III) is obtained by crystallization from 30% water in acetone or by grinding any other form under water.
>
> A hemihydrate form of cortisone acetate (Form IV) is produced by crystallizing from ethanol containing a lesser amount (5%) of water than is used to produce anhydrous Form III.
>
> A monohydrate form of cortisone acetate (Form V) is obtained by

> recrystallization from a 3:1 mixture of carbon tetrachloride and methanol, but only if the methanol is anhydrous. If the methanol contains more than 2% water cortisone acetate will crystallize in the hemihydrate form. This trend is the reverse of what would be expected if there were a simple positive correlation between the hydration state of the crystal and the amount of water present in the recrystallization solvent system. Carless, J.E. et. al *J. Pharm Pharmacol.* 1966, *18*, 1905 ("Carless," Exh. 7).
>
> Anhydrous caffeine Form I may be prepared by heating anhydrous caffeine Form II to 180°C, while anhydrous caffeine Form II may be prepared by recrystallization from water. Pirttimaki, J.; Laine, E. *European J. of Pharm. Sci.* **1994**, *1*, 203-208, 204. ("Pirttimaki," Exh. 8).

Examples like these of the unpredictability of the solid-state behavior of compounds illustrate the unpredictability of the result obtained by contacting a solid organic compound with a particular solvent.

One respected authority in the field describes procedures that may be tried to produce a particular hydrate of a compound.

> Typically, hydrates are obtained by recrystallization from water [example omitted]. Hydrates can sometimes be obtained by simply suspending the anhydrous material in water, whereupon a form of Ostwald ripening occurs [Example omitted]. In other instances, hydrates can be obtained from mixed solvent systems [Example omitted]. Simply exposing an anhydrous powder to high relative humidity can often lead to formation of a hydrate.

Brittain, Exh. 3, p. 204.

However, Applicants respectfully submit that none of these methods can be predicted to yield an organic compound in a particular state of hydration.

According to the Examiner, claims 5-7 directed to a process for preparing ondansetron hydrochloride monohydrate do not yield a novel material. In Wu Gousheng, the monohydrate is allegedly obtained by crystallization from water and by dehydration of the dihydrate under vacuum over P_2O_5. Applicants' claim 5 calls for contacting ondansetron hydrochloride

dihydrate with an ethanol and water mixture. Applicants respectfully submit that one of ordinary skill in the art who was familiar with the teachings of Wu Gousheng would not expect to obtain the monohydrate by contacting the dihydrate with this solvent mixture even if Wu Gousheng motivated them to try, which it does not do. There is no way to know *a priori* whether contacting ondansetron hydrochloride dihydrate with an ethanol and water mixture would change the hydration state of ondansetron hydrochloride dihydrate or produce unsolvated material or even produce a different solvate. For these reasons, Applicants' respectfully submit that the rejection of claims 5-7 for obviousness over Wu Gousheng is improper and request that it be withdrawn.

Claim 8 is directed to a process for preparing ondansetron hydrochloride dihydrate Form A by hydrating the monohydrate under an atmosphere of 50% relative humidity or greater. Nowhere in Wu Gousheng is there a teaching or suggestion that ondansetron hydrochloride monohydrate could be converted to the dihydrate under such conditions. Applicants further respectfully submit that the dehydration of the dihydrate to obtain the monohydrate under extremely desicating conditions (P_2O_5, vacuum) does not lead one skilled in the art to expect to be able to produce ondansetron hydrochloride monohydrate from the dihydrate by placing it under an atmosphere of 50% relative humidity or greater. The fact that dry air can remove water from the dihydrate does not imply that the monohydrate will absorb water from moist air to yield a dihydrate. For the foregoing reasons, reconsideration and withdrawal of the rejection of claim 8 for obviousness over Wu Gousheng is respectfully requested.

The rejection of claims 10-18 is improper for essentially the same reason that rejection of claims 5-7 is improper. One of ordinary skill in the art would not *a priori* have a reasonable expectation of success producing Form A by the processes recited in those claims, which

include particular solvents that Applicants have discovered produce Form A under the conditions defined by those claims. Regarding the preferred use of sonication to prepare Form A in claim 18, the Examiner asserts that one of ordinary skill has a blanket motivation to use sonication as a mechanical expedient to accelerate the process for preparing Form A. Applicants respectfully question whether one skilled in the art with the benefit of Applicants disclosure that ondansetron hydrochloride dihydrate could be dehydrated to yield ondansetron hydrochloride Form A would immediately turn to sonication as a matter of expediency to obtain improved results.

Claim 24 is directed to a method of treating nausea and/or vomiting with a pharmaceutical composition of claim 23, as amended, comprising anhydrous ondansetron hydrochloride. and/or ondansetron hydrochloride Form B. Claim 24 was rejected over Wu Gousheng for obviousness.

> Interpreting the claimed invention as a whole requires consideration of all claim limitations. Thus proper claim construction requires treating language in a process claim which recites the making or using of a nonobvious product as a material limitation. Motivation to make or use the nonobvious product must be present in the prior art for a 35 U.S.C. 103 rejection to be sustained. The decision in *Ochiai* specifically dispelled any distinction between processes of making a product and methods of using a product with regard to the effect of any product limitations in either type of claim.

MPEP 2116.01 (8th ed. Rev. Feb. 2003).

Here, the cited reference fails to provide any motivation or suggestion to: i) prepare a pharmaceutical composition comprising the claimed ondansetron hydrochloride Form B and ii) use such a pharmaceutical composition to treat nausea and/or vomiting. Accordingly, Applicants respectfully request reconsideration and withdrawal of the 35 U.S.C.§ 103 rejection.

Claims 25-38 are directed to a process for preparing anhydrous ondansetron hydrochloride and Form B by treating ondansetron hydrochloride with a dry alcohol. The § 103 rejection of claims 25-38 over Wu Gousheng is improper, *inter alia*, for reasons similar to the reasons that the rejection of claims 5-7 is improper. One skilled in the art would not expect *a priori* that he or she could produce anhydrous ondansetron hydrochloride by treating ondansetron hydrochloride in any state of hydration with dry alcohol. Such treatment could leave the monohydrate or dihydrate unchanged or change them in an unpredictable way. For example, from a solution containing ondansetron, chloride anion and water originating from the dissolved hydrate and alcohol (that initially was dry before dissolving of the ondansetron hydrochloride), it is conceivable that any of the following would be the least soluble and therefore precipitate from the solution: anhydrous ondansetron free base, a hydrate of ondansetron free base, an alcohol solvate of ondansetron free base, an ondansetron hydrochloride hydrate, an ondansetron hydrochloride alcohol solvate or, as found by the Applicants, anhydrous ondansetron hydrochloride. The effect of crystallization of ondansetron under such conditions is not predictable (and, therefore, not within the level of ordinary skill in the art) and is not taught by the cited reference. Yet further, it is not predictable or taught by Wu Gousheng that one could obtain a novel solid state form of ondansetron by treating ondansetron hydrochloride with dry alcohol. Whereas anhydrous ondansetron hydrochloride and Form B are non-obviousness, Applicants further submit that the art does not provide the required motivation to make these materials, whose possible existence was unknown at the time of Applicants' invention. For each of the foregoing reasons, independently, the rejection of claims 25-38 under § 103 cannot be sustained.

Claims 46-48, directed to a process for preparing ondansetron hydrochloride Form B by reacting HCl gas with a toluene solution of ondansetron free base, have been rejected for

obviousness over Wu Gousheng. The Examiner appears to rely upon the portion of Wu Gousheng's specification which states ". . . .the chemical compound with general formula (II) or a mixture with a content of greater than 30% is continuously added to a water-alcohol solvent, while at the same time passing through chlorinated hydrogen and other gasses, making it possible to obtain the chemical compound of general formula (I) in a continuous manner." (p. 2 of translation, 3rd full paragraph). Wu Gousheng does not teach or suggest using gaseous HCl to prepare the hydrochloride salt in toluene, let alone that one would obtain the unexpected result of producing a novel polymorph of ondansetron hydrochloride. Applicants respectfully submit that these are critical deficiencies in the reference. As previously stated, all solvents are not functionally equivalent. Moreover, there are many solvents from which to choose a solvent for generating the hydrochloride salt from ondansetron free base. Yet, there is no guidance in Wu Gousheng or anywhere in the art to Applicants' knowledge that a novel polymorphic form of ondansetron hydrochloride having the characteristics of Form B could be obtained by selecting toluene as the solvent. Without such guidance, the motivation for selecting toluene is lacking. Without motivation to modify Wu Gousheng to arrive at Applicant's process, Wu Gousheng cannot render obvious Applicants' claims to that process. *In re Fine*, 5 U.S.P.Q.2d (BNA) 1596, 1599 (Fed. Cir. 1988). Therefore, reconsideration and withdrawal of the rejection of claims 46-48 is respectfully requested.

Claim 51, directed to a process for preparing ondansetron hydrochloride Form C, was rejected for obviousness over Wu Gousheng. In making the rejection, the Examiner appears to disregard the particular steps of the process that enable preparation of novel Form C. Of note, ondansetron free base is dissolved in ethanol and contacted with an ethanolic solution of HCl. The mixture is then filtered to remove solids and, then, the filtrate is evaporated leaving ondansetron hydrochloride in a novel solid state that gives a unique X-ray diffraction pattern,

which Applicants have denominated Form C. A similar manipulation that Wu Gousheng performs is suspending ondansetron free base in ethanol in preparation for adsorbing it onto a cationic exchange resin in Embodiment A_2, after which the ondansetron presumably dissolves attendant to its becoming adsorbed onto the resin. However, Wu Gousheng obtains ondansetron hydrochloride monohydrate at the conclusion of this process by deadsorbing ondansetron with aqueous hydrochloric acid. He does not obtain novel Form C. There is no specific or general teaching in Wu Gousheng to modify Embodiment A_2 to arrive at Applicants' process and certainly no expectation that one would obtain a novel crystalline form of ondansetron hydrochloride by doing so. Therefore, reconsideration and withdrawal of the obviousness rejection of claim 51 over Wu Gousheng is respectfully requested.

Claims 42-56, directed to a process for preparing novel ondansetron hydrochloride Form D, were rejected for obviousness over Wu Gousheng. In Applicants' process, ondansetron hydrochloride is melted in the presence of xylene and the melt is added to cooled ethanol, e.g. -10°C. This addition causes rapid cooling and precipitation of ondansetron hydrochloride in novel Form D, which produces a unique PXRD pattern. Again, the rejection disregards the process delineated by the claims, suggesting to the Applicants' that the rejection could only be supported by hindsight application of the knowledge conferred by the Applicants. Nowhere in Wu Gousheng is there a teaching or suggestion of melting ondansetron hydrochloride in the presence of xylene and then adding the melt to ethanol in order to produce a new form. If the Examiner believes that motivation to perform these manipulative steps is to be found in the art or within the skill level of the artisan, documentation of the underlying knowledge that would provide such motivation is requested. Applicants respectfully submit that claims 42-56 are non-obvious over Wu Gousheng and request withdrawal of the § 103 rejection of those claims.

Claims 59-61, directed to a process for preparing ondansetron hydrochloride Form E, were rejected for obviousness over Wu Gousheng. Form E is a novel solid state of ondansetron hydrochloride and is identifiable by its PXRD pattern. According to Applicants' process, Form E is prepared by treating ondansetron hydrochloride with isopropanol. Wu Gousheng does not teach or suggest treating ondansetron hydrochloride with isopropanol. While isopropanol is a well known solvent, it has been found by the Applicants to be functionally dissimilar to the solvents with which ondansetron hydrochloride is brought into contact in Wu Gousheng, *inter alia*, because treatment of ondansetron hydrochloride with isopropanol produces a novel crystalline form. Lacking a teaching or suggestion to motivate one skilled in the art to modify Wu Gousheng to arrive at Applicants' claim process, Wu Gousheng does not render obvious claims 59-61. Accordingly, Applicants respectfully request withdrawal of the § 103 rejection of claims 59-61.

Claims 68-70, directed to the preparation of novel ondansetron hydrochloride Form H, were rejected for obviousness over Wu Gousheng. Steps (a) and (b) of Applicants' process for making Form H are identical to steps (a) and (b) of their process for making Form C, which result in a solution of ondansetron and hydrogen chloride in ethanol. In this process, however, addition of ether to induce precipitation of the hydrochloride salt yields it in a novel solid state that produces a unique PXRD pattern, which Applicants have denominated Form H. Wu Gousheng does not teach or suggest precipitation of ondansetron hydrochloride from any solvent by the addition of any other liquid organic compound, like ether, whose addition would reduce the solubility of ondansetron hydrochloride in the solvent (referred to as an "anti-solvent"). Rather, in Wu Gousheng, ondansetron hydrochloride was crystallized from water, presumably by allowing the solution to stand without any other manipulation. Should the Examiner consider the use of an anti-solvent to be an "expedient" akin to sonication,

Applicants respectfully submit that there are many anti-solvents from which to choose and that the selection of ether is nowhere taught or suggested in Wu Gousheng, let alone that its selection would cause ondansetron hydrochloride to precipitate in a novel solid state. For the foregoing reasons, Applicants respectfully submit that neither Wu Gousheng, nor any express disclosure in the art of which Applicants are aware, nor the knowledge possessed by those skilled in the art would suggest modification of Wu Gousheng to arrive at the process claimed in claims 68-70. Therefore, Applicants respectfully request withdrawal of the § 103 rejection of those claims.

Claims 77-86, directed to the preparation of novel ondansetron hydrochloride Form I, were rejected for obviousness over Wu Gousheng. In Applicants' process, Form I is prepared by exposing ondansetron hydrochloride to methanol vapor. Wu Gousheng does not teach or suggest exposing ondansetron hydrochloride to methanol as a way of transforming it into a novel solid state form. Although Brittain teaches that "exposing an anhydrous powder to high relative humidity can often lead to formation of a hydrate," Brittain, p.204, applicants respectfully submit that Brittain does not create in the mind of the skilled practitioner a reasonable expectation of being able to effect the conversion of ondansetron hydrochloride in another solid state form into Form I with a reasonable likelihood of success. Accordingly, Applicants respectfully submit that Wu Gousheng does not render obvious Applicants' process and, therefore, that rejection of claims 77-86 should be withdrawn.

Claim 92 is directed to a method of treating nausea and/or vomiting by administering a therapeutically effective amount of a novel pharmaceutical composition claimed in claim 91 comprising ondansetron with a particle size distribution with an upper limit of 50 microns. Claim 92 also was rejected over Wu Gousheng. For reasons discussed above, the rejection of claim 91 under § 102 is not properly supported. Applicants respectfully submit that use of that

patentable composition, even for a purpose for which ondansetron hydrochloride is known to be useful, is non-obvious. In *In re Ochiai*, 71 F.3d 1565 (Fed. Cir. 1995), the Federal Circuit concluded that a claim to a process for preparing a cephem compound using a conventional process on novel starting material was non-obvious where the prior art did not teach or suggest the starting material. In the court's words:

> The process invention Ochiai recites in claim 6 specifically requires use of none other than its new, nonobvious acid as one of the starting materials. One having no knowledge of this acid could hardly find it obvious to make any cephem using this acid as an acylating agent, much less the particular cephem recited in claim 6. In other words, it would not have been obvious to those of ordinary skill in the art to choose the particular acid of claim 6 as an acylating agent for the known amine for the simple reason that the particular acid was unknown but for Ochiai's disclosure in the '429 application.
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> [A]lthough the prior art references the examiner discussed do indeed teach the use of various acids to make various cephems, they do not define a class of acids, the knowledge of which would render obvious the use of Ochiai's specifically claimed acid.[fn omitted] The Board noted that Ochiai's specifically claimed acid is "similar" to the acids used in the prior art. Likewise, the examiner asserted that the claimed acid was "*slightly* different" form those taught in the cited references. Neither characterization, however, can establish the obviousness of the use of a starting material that is new and nonobvious, both in general and in the claimed process.

Id. 71 F. 3d at 1569, 1570 (emphasis in original)

Here, the cited reference fails to provide any motivation or suggestion to: i) prepare a pharmaceutical composition comprising the claimed ondansetron hydrochloride with an upper particle size limit of 50 microns and ii) use such a pharmaceutical composition to treat nausea

and/or vomiting. For the foregoing reason, the rejection of claim 92 under § 103 is improper and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully submits that claims 5-8 and 10-93 are in condition for allowance. Early and favorable action by the Examiner is earnestly solicited. If the Examiner believes that issues may be resolved by a telephone interview, the Examiner is urged to telephone the undersigned at the number below. The undersigned may also be contacted by email at pjohnson@kenyon.com.

Respectfully Submitted,

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Dated: 7/7/03

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Marked Up Versions of Amended Claims

22. (Amended) Ondansetron hydrochloride Form B characterized by powder X-ray diffraction peaks at 10.5, 11.9, [10.5,] 13.0, 13.5, 15.1, 20.9, 22.7, 24.0, and 25.7 ±0.2 degrees two-theta.

23. (Amended) A pharmaceutical composition comprising the ondansetron hydrochloride of any one of claims [1]19 through 22 and a pharmaceutically acceptable carrier.

72. (Amended) [Ondansetrion] Ondansetron hydrochloride methanolate.